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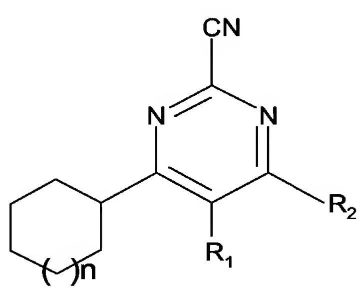
(54) Title: 4-CYCLOALKYL-PYRIMIDINE-2-CARBONITRILE DERIVATIVES



(I)

(57) Abstract: The invention relates to 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives having the general formula (I) wherein n is 0, 1, 2 or 3; R_1 is H or (C_{1-6})alkyl; R_2 is (C_{2-6})alkyl, optionally substituted with one or more halogens, OH, (C_{1-4})alkyloxy or NR_3R_4; R_3 and R_4 are independently H, (C_{1-4})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl(C_{1-4})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-9})heteroaryl, (C_{2-9})heteroaryl(C_{1-4})alkyl or (C_{1-4})alkyl substituted with a 4-8 membered saturated heterocyclic ring comprising 1-3 heteroatoms selected from O, S and NR_5; or R_3 and R_4 together with the nitrogen to which they are bound form a 4-8 membered saturated heterocyclic ring, which ring optionally comprises NR_5, and which ring is optionally substituted with (C_{6-10})aryl, (C_{6-10})aryloxy, (C_{6-10})aryl(C_{1-4})alkyloxy, (C_{2-9})heteroaryl, NR_6,R_7, $CONR_6R_7$ or NR_6COR_7; R_5 is H, (C_{1-4})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-5}) heteroaryl or (C_{2-5})heteroaryl(C_{1-4})alkyl; R_6 and R_7 are independently H or (C_{1-4})alkyl; or a pharmaceutically acceptable salt thereof. The invention also relates to pharmaceutical compositions comprising said compounds as well as to the use thereof in the treatment of osteoporosis, atherosclerosis and related disorders.

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4-CYCLOALKYL-PYRIMIDINE-2-CARBONITRILE DERIVATIVES

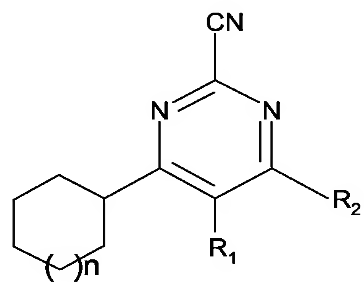
The invention relates to 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives, to pharmaceutical compositions comprising the same, as well as to the use of these derivatives for the preparation of a medicament for the treatment of cathepsin K related diseases such as osteoporosis and atherosclerosis.

Cysteine proteases represent a class of peptidases characterised by the presence of a cysteine residue in the catalytic site of the enzyme, and these proteases are associated with the normal degradation and processing of proteins. Many pathological disorders or diseases are the results of abnormal activity of cysteine proteases such as over expression or enhanced activation. The cysteine cathepsins, e.g. cathepsin B, K, L, S,V, F, are a class of lysosomal enzymes which are implicated in various disorders including inflammation, rheumatoid arthritis, osteoarthritis, osteoporosis, tumors, coronary disease, atherosclerosis, autoimmune diseases and infectious diseases.

Cathepsin K has strong collagenolytic, elastase and gelatinase activities (Bromme et al., J. Biol, Chem, 271, 2126-2132, 1996) and is predominantly expressed in osteoclasts (Bromme and Okamoto, Biol. Chem. Hopp-Seyler, 376, 379-384, 1995). It cleaves key bone matrix proteins, including collagen type I and II (Kaffienah et al., Biochem. J. 331, 727-732, 1998), gelatine, osteopontin and osteonectin, and as such is involved in extracellular matrix metabolism necessary for normal bone growth and remodelling (Bossard et al., J. Biol. Chem. 271, 12517-12524, 1996). Inhibition of cathepsin K should result in the diminuation of osteoclast mediated bone resorption. Cathepsin K inhibitors may therefore represent new therapeutic agents for the treatment of disease states in man such as osteoporosis.
Sukhova et al (J. Clin. Invest. 102, 576-583, 1998) have thereafter demonstrated that cells (macrophages) that migrate into and accumulate within developing human atherosclerotic plaques also synthesize the potent elastases Cathepsin K and S. Matrix degradation, particularly in the fibrous cap of such plaques, is a crucial process in atherosclerotic lesion destabilization. Thus, the metabolism of the extracellular matrix components collagen and elastin, which confer structural integrity upon the lesion's fibrous cap, can critically influence the clinical manifestations of atherosclerosis, such as coronary artery thrombosis as a result of rupture of an atherosclerotic plaque. Inhibition of cathepsins K and/or S at sites of plaques prone to rupture may thus represent an effective way of preventing such events.

4-Amino-pyrimidine-2-carbonitrile derivatives have been disclosed as inhibitors of cathepsins K in the International Patent Application WO 03/020278 (Novartis Pharma GMBH) and WO04/020441 (Novartis Pharma GMBH), while structurally related 4-amino-pyrimidine-2 carbonitrile derivatives were recently disclosed in WO04/000819 (ASTRAZENECA AB) as Cathepsin S inhibitors.

It has now been found that 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives having the general formula I



Formula I

wherein

n is 0, 1, 2 or 3;

R_1 is H or (C_{1-6})alkyl;

R_2 is (C_{1-6})alkyl, optionally substituted with one or more halogens, OH, (C_{1-4})alkyloxy or NR_3R_4;

R_3 and R_4 are independently H, (C_{1-4})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl(C_{1-4})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-9})heteroaryl, (C_{2-9})heteroaryl(C_{1-4})alkyl or (C_{1-4})-alkyl substituted with a 4-8 membered saturated heterocyclic ring comprising 1-3 heteroatoms selected from O, S and NR_5; or

R_3 and R_4 together with the nitrogen to which they are bound form a 4-8 membered saturated heterocyclic ring, which ring optionally comprises NR_5, and which ring is optionally substituted with (C_{6-10})aryl, (C_{6-10})aryloxy, (C_{6-10})aryl(C_{1-4})alkyloxy, (C_{2-9})-heteroaryl, NR_6,R_7, $CONR_6R_7$ or NR_6COR_7;

R_5 is H, (C_{1-4})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-5})heteroaryl or (C_{2-5})-heteroaryl(C_{1-4})alkyl;

R_6 and R_7 are independently H or (C_{1-4})alkyl;

or a pharmaceutically acceptable salt thereof; are inhibitors of cathepsin K and can therefor be used for the preparation of a medicament for the treatment of osteoporosis, atherosclerosis and related Cathepsin K dependent disorders.

The term (C_{1-6})alkyl, as used in the definition of formula I, means a branched or unbranched alkyl group having 1-6 carbon atoms, like hexyl, pentyl, 3-methyl-butyl, butyl, isobutyl, tertiary butyl, propyl, isopropyl, ethyl and methyl. A preferred (C_{1-6})alkyl, as used in the definition of R_2 in formula I, is n-propyl.
The term (C_{1-4})alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, like butyl, isobutyl, tertiary butyl, propyl, isopropyl, ethyl and methyl.
The term (C_{3-8})cycloalkyl means a cycloalkyl group having 3-8 carbon atoms, such as cyclooctyl, cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.
The term (C_{6-10})aryl means a radical derived from an aromatic group having 6-10 carbon atoms like for example phenyl and naphthyl.

The terms (C_{6-10})aryl(C_{1-4})alkyl means a (C_{1-4})alkyl group which is substituted with a (C_{6-10})aryl group, like for example the benzyl group.
The term (C_{2-9})heteroaryl means a 5 or 6-membered cyclic aromatic group having 1-3 heteroatoms selected from nitrogen, oxygen or sulfur, optionally fused to a benzo-group. Examples of (C_{2-9})heteroaryl groups are pyridyl, imidazolyl, furanyl, pyrazolyl, pyrimidinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, quinolyl, isoquinolyl, benzofuranyl, benzothiazolyl, benzimidazolyl, and the like. Preferred heteroaryl groups are 2-pyridyl and 3-pyridyl.
The term (C_{2-9})heteroaryl(C_{1-4})alkyl means a (C_{1-4})alkyl group which is substituted with a (C_{2-9})heteroaryl group, like for example a pyridin-4-ylmethyl group.
The term (C_{2-5})heteroaryl means a 5 or 6-membered cyclic aromatic group having 1-3 heteroatoms selected from nitrogen, oxygen or sulfur. Examples of such (C_{2-5})heteroaryl groups are pyridyl, imidazolyl, furanyl, pyrazolyl, pyrimidinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl and oxadizolyl.
In the definition of formula I R_3 and R_4 can form together with the nitrogen to which they are bound a 4-8 membered saturated heterocyclic ring, such as an azetidine, a pyrrolidine, a piperidine, or a 1H-azepine ring. Such rings may contain 1 or more additional heteroatoms selected from O, S or NR_5 to form rings such as a morpholine, a thiomorpholine, a hexahydro-1,4-oxazepine, a piperazine, a homo-piperazine, an imidazolidine or a tetrahydrothiazole ring.
The term halogen means F, Cl, Br, or I. When halogen is a substituent at an alkyl group, F is preferred. A preferred halogen substituted alkyl group is trifluoromethyl.

Preferred in the invention are those 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives according to formula I wherein R_1 is H and R_2 is (C_{1-6})alkyl substituted with OH, one or more halogens, (C_{1-4})alkyloxy or NR_3R_4.

Further preferred are the compounds wherein R_2 is n-propyl substituted at the 3-position with NR_3R_4.

More preferred are the derivatives of formula I wherein the 4-cycloalkyl group is cycloheptyl (n=2).

Especially preferred 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of the invention are:

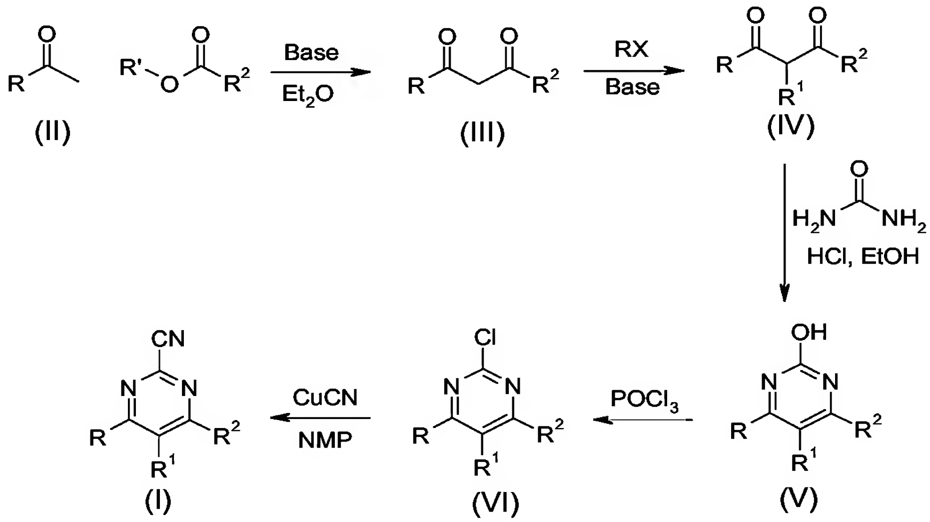
- 4-cycloheptyl-6-[3-(3-phenyl-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-pyridin-2-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-piperidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-(3-cyclohexylamino-propyl)-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-morpholin-4-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-pyrrolidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile; and
- 4-cycloheptyl-6-[3-(3-diethylamino-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile;

The invention provides in a further aspect pharmaceutical compositions comprising a 4-cycloallkyl-pyrimidine-2-carbonitrile derivative having general formula I, or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable auxilliaries.

The 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of general Formula I may be prepared by, as depicted in Scheme 1, by condensation of a methyl ketone derivative having formula (II), wherein R represents a (C_{5-8})cycloalkyl group, with an ester of formula R'-OC(O)R_2, wherein R' represents a (C_{1-6})alkyl group and R_2 is as previously defined, to form a 1,3-dione derivative of formula (III). R' and R_2 can also be part of 5-8 membered rings formed together with the ester function to which they bound. Optionally, the group R_1 can be introduced by alkylation of the 1,3-dione derivative in the presence of a base, e.g. potassium carbonate, and a suitable solvent, e.g. THF or acetone with heating, to provide a 2-alkyl-1,3-dione derivative having formula (IV). Cyclisation of the 1,3-dione (IV) with urea in the presence of an acid, e.g. concentrated aqueous hydrochloride in a suitable solvent, e.g. ethanol with heating, produces the 2-hydroxy-4-cycloalkyl-pyrimidine derivative of formula (V). Treatment of a compound of formula (V) with $POCl_3$ under heat provides the 2-chloro-4-cycloalkyl -pyrimidine derivative of formula (VI), which upon cyanation with cuprous cyanide in solvent, e.g. dimethylformamide or N-methylpyrrolidinone and with the help of microwave heating provides a 4-cycloalkyl-pyrimidine-2-carbonitrile derivative of general Formula I.

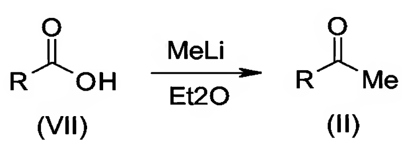
The cyanation step can also be performed with zinc cyanide as reagent with transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium in a suitable solvent, e.g. dimethylformamide, dimethoxyethane or N-methylpyrrolidinone.

Scheme 1



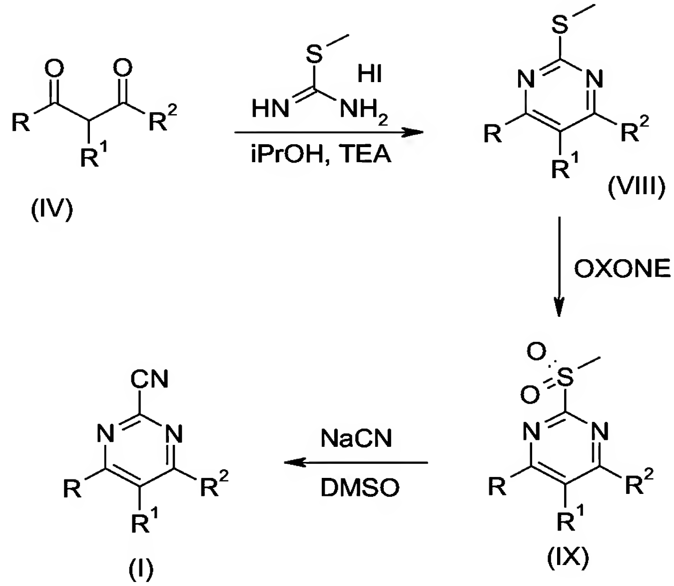
The above mentioned methyl ketone (II) can be synthesized from the corresponding carboxylic acid by treating with methyl lithium (Scheme 2).

Scheme 2



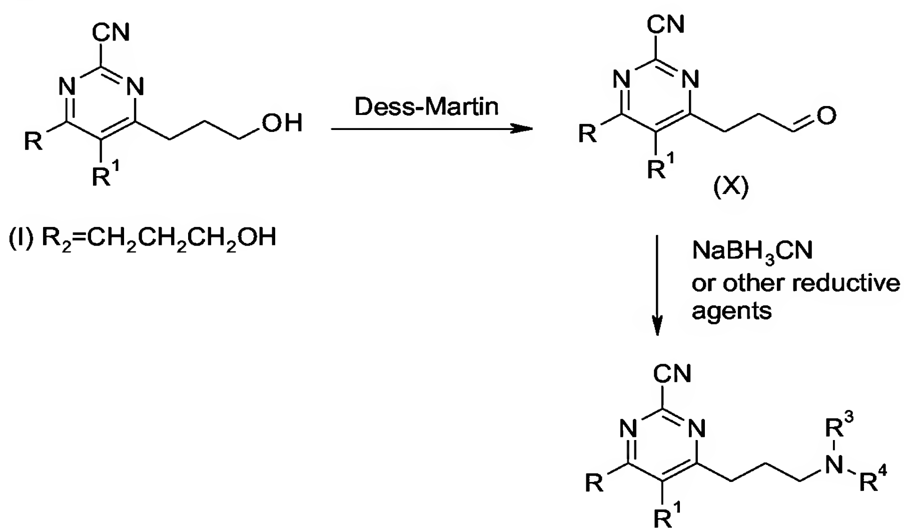
In an alternative method, as depicted in Scheme 3, a 1,3-dione derivative of formula (IV) is treated with S-methyl isothiourinium iodide neat or in a suitable solvent, e.g. isopropanol, and a suitable base, e.g. triethyl amine, to give a 2-methylsulfanyl-4-cycloalkyl-pyrimidine derivative of formula (VIII). Oxidation of a derivative of formula VIII with potassium monopersulfate (Oxone) or m-chloroperbenzoic acid (MCPBA) in a suitable solvent, e.g. methanol, water, chloroform or a mixture thereof, provides a 2-methanesulphonyl-4-cycloalkyl-pyrimidine derivative of formula (IX), which upon treatment with sodium cyanide in a suitable solvent, e.g. dimethylsulfoxide yields a 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of general Formula I.

Scheme 3



The 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of general Formula I, wherein R_2 represents a (C_{1-6})alkyl group substituted with NR_3R_4, can advantageously be prepared starting from the corresponding alcohol derivative as depicted in scheme 4 for compounds of the invention in which R_2 represent a 3-OH-propyl substituent. Oxidation of the pertinent alcohol derivative of fomula (I) with Dess-Martin periodinane, or using an alternative oxidation procedure, provides the corresponding aldehyde derivative according to formula (X), which is subsequently condensed with an amine of formula HNR_3R_4 under reductive amination conditions to produce said 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of the invention.

Scheme 4



In the preparation of a 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of general Formula I in which the R_2 group contains a basic amine nitrogen atom (either in the form of NR_3R_4 or NR_5), such a nitrogen is to be temporarily protected, such as for example by the acid labile t-butyloxycarbonyl (Boc) group protecting group. Other suitable protecting groups for functional groups which are to be temporarily protected during syntheses, are known in the art, for example from Wuts, P.G.M. and Greene, T.W.: *Protective Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999.

The compounds of the invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as, but not limited to, hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

Compounds of the invention may exist in solvated as well as in unsolvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Compounds of the present invention may exist as amorphous forms, but also multiple crystalline forms may be possible. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of this invention.
The 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives of the invention and their salts may contain a centre of chirality in one or more of the side chains R_1-R_5, and may therefore be obtained as a pure enantiomer, or as a mixture of enantiomers, or as a mixture containing diastereomers. Methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, e.g. synthesis with chiral induction or starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers or enantiomers using chromatography on chiral media. Such methods are for example described in *Chirality in Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley).

The compounds of the inventioin were found to be inhibitors of human Cathepsin K and can therefore in a further aspect of the invention be used in therapy, and

especially for the preparation of a medicament for the treatment of osteoporosis, atherosclerosis and related Cathepsin K dependent disorders.

The compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0.001-100 mg per kg body weight, preferably 0.01-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing) the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied in the form of a solution, suspension, emulsion, e.g. for use as an injection preparation, or as a spray, e.g. for use as a nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts.

The invention is further illustrated by the following examples.

Methods

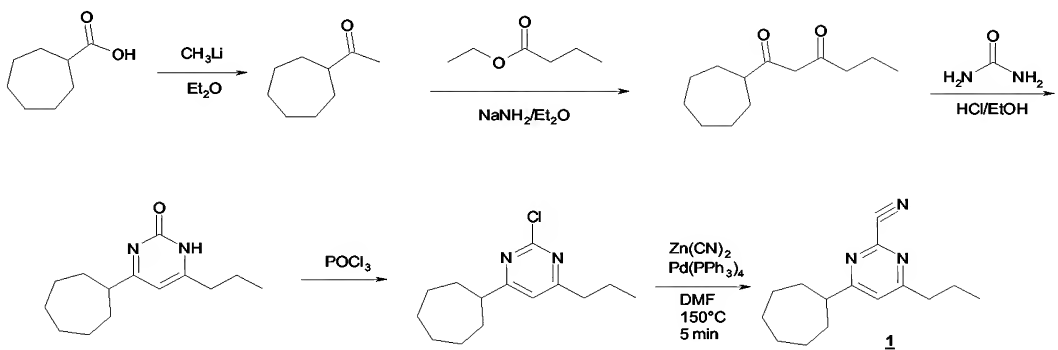
General Chemical Procedures. All reagents were either purchased from common commercial sources or synthesised according to literature procedures using commercial sources. Proton NMR (^1H NMR) were obtained on a Bruker DPX 400 spectrometer and are referenced to internal TMS. Mass spectra were recorded on a Shimadzu LC-8A (HPLC) PE Sciex API 150EX LCMS. Analytical reversed-phase LCMS analysis was carried out on LUNA C18 column (5μ; 30 x 4.6 mm) under gradient conditions (90% water / 0.1% formic acid to 90% acetonitrile / 0.1% formic acid) at a flow rate of 4 ml/min.

Abbreviations

Dimethylformamide (DMF), N-methylpyrolidinone (NMP), dichloromethane (DCM), dimethylsufoxide (DMSO), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), high pressure liquid chromatography (HPLC), diisopropylethylamine (DIPEA), triethylamine (TEA), broad (br), singlet (s), doublet (d), triplet (t), trifluoroacetic acid (TFA), tert-butyloxycarbonyl (Boc).

EXAMPLE 1.

1: 4-Cycloheptyl-6-propyl-pyrimidine-2-carbonitrile



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A: 1-cycloheptyl-ethanone

To a stirred solution of cycloheptanecarboxylic acid (22 g) in ether (500 mL) at 0°C under nitrogen was added over 60 minutes a solution of methyl lithium in ether (200 mL, 1.6M). After 30 minutes, the suspension was allowed to warm to room temperature and stirred overnight. The suspension was added slowly to a stirred mixture of ice-water (500 mL) and HCl (250 mL, 2M). The organic layer was separated, washed with water (100 mL), sodium carbonate solution (100 mL), then water (2 x 100 mL), dried over sodium sulphate and evaporated at reduced pressure to afford 1-cycloheptyl-ethanone as an oil (17.8 g).

^{1}H NMR ($CDCl_3$): δ 2.52 (m, 1H), 2.13 (s, 3H), 1.86 (m, 2H), 1.72 (m, 2H), 1.43-1.61 (m, 8H).

B: 1-cycloheptyl-hexane-1,3-dione

To a stirred suspension of sodium amide (0.62 g) in ether (50 mL) under nitrogen was added slowly a solution of 1-cycloheptyl methyl ketone (1.0 g) in ether (10 mL). The mixture was stirred for 10 minutes, than a solution of ethyl butyrate (0.94 mL) in ether (10 mL) was added slowly. The mixture was heated at reflux for 2 hours, then was allowed to cool to room temperature and stirred overnight. The mixture was poured into stirred water (70 mL) and acidified with HCl (2M). The aqueous layer was separated and extracted with ether (40 mL). the organic layers were combined, washed with water (3 x 50 mL), dried over sodium sulphate and evaporated at reduced pressure to give the crude product as an oil (1.42 g). Flash chromatography on silica afforded 1-cycloheptyl-hexane-1,3-dione as an oil (0.45 g).

^{1}H NMR ($CDCl_3$): δ 15.57 (bs, 0.9H), 5.45 (s, 0.9H), 3.58 (s, 0.2H), 2.32 (m, 1H), 2.25 (t, 2H), 1.87 (m, 2H), 1.75 (m, 2H), 1.42-1.68 (m, 10H), 0.95 (t, 3H). MS *m/z:* 211.3 (M+1), 100%.

C: 4-cycloheptyl-6-propyl-1*H*-pyrimidin-2-one

A stirred mixture of 1-cycloheptyl-hexane-1,3-dione (420 mg), urea (180 mg), HCl (0.3 mL, 5M) and ethanol (10 mL) was heated at reflux overnight. Further urea (180 mg) and HCl (0.3 mL, 5M) were added and stirring was continued at reflux overnight. The mixture was allowed to cool and the solvent was evaporated at reduced pressure. The residue was dissolved in a mixture of ethyl acetate and water. The aqueous layer was separated, washed with ethyl acetate to remove residual 1-cycloheptyl-hexane-1,3-dione, then extracted with DCM (5X). The combined DCM extracts were washed with water, dried over sodium sulphate and evaporated at reduced pressure to afford 4-cycloheptyl-6-propyl-1*H*-pyrimidin-2-one as a gum (150 mg). ^1H NMR ($CDCl_3$): δ 13.20 (bs, 1H), 6.01 (s, 1H), 2.69 (m, 1H), 2.58 (t, 2H), 1.93 (m, 2H), 1.46-1.86 (m, 12H), 0.98 (t, 3H). MS *m/z:* 235.3 (M+1), 100%.

D: 2-chloro-4-cycloheptyl-6-propyl-pyrimidine

A mixture of 4-cycloheptyl-6-propyl-1*H*-pyrimidin-2-one (130 mg) and phosphorus oxychloride (2 mL) was stirred and heated at reflux overnight, then allowed to cool and poured on to ice. The mixture was extracted with ether and the organic extract was washed with saturated sodium carbonate solution, then with water (3X), dried over sodium sulphate and evaporated at reduced pressure to afford 2-chloro-4-cycloheptyl-6-propyl-pyrimidine as a viscous oil (115 mg). ^1H NMR ($CDCl_3$): δ 6.90 (s, 1H), 2.79 (m, 1H), 2.68 (t, 2H), 1.94 (m, 2H), 1.50-1.87 (m, 12H), 0.97 (t, 3H). MS *m/z:* 253.1 (M+1), 100%.

E: 4-cycloheptyl-6-propyl-pyrimidine-2-carbonitrile

A mixture of 2-chloro-4-cycloheptyl-6-propyl-pyrimidine (50 mg), zinc cyanide (23 mg) and tetrakis(triphenylphosphine)palladium(0) (23 mg) in DMF (1 mL) was heated in a microwave at 150°C for 5 minutes. The mixture was diluted with ethyl acetate (20 mL) and the solution was washed with water (5 x 10 mL), dried over sodium sulphate and evaporated at reduced pressure to give the crude product as a gum (65 mg). Preparative-HPLC afforded 4-cycloheptyl-6-propyl-pyrimidine-2-carbonitrile as a gum (21 mg). ^1H NMR ($CDCl_3$): δ 7.12 (s, 1H), 2.84 (m, 1H), 2.73 (t, 2H), 1.48-1.99 (m, 14H), 0.98 (t, 3H). MS *m/z:* 244.6 (M+1), 100%.

EXAMPLE 2.

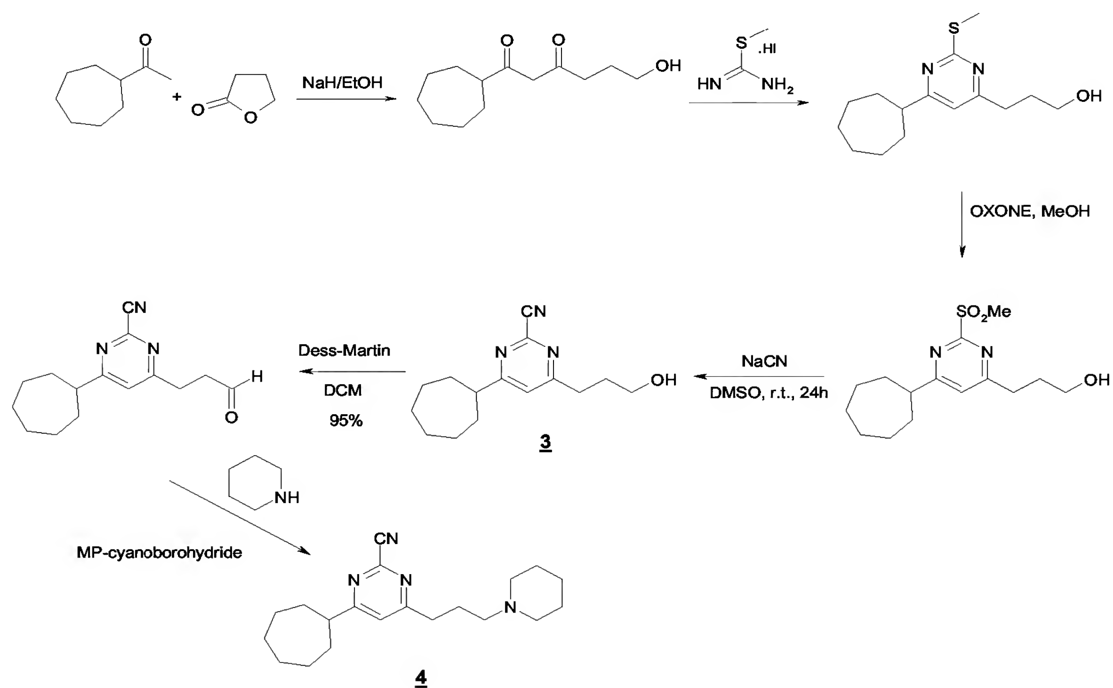
The procedure described in Example 1 was further applied, starting with cyclohexyl methyl ketone, to prepare the following compound:

2: 4-cyclohexyl-6-propyl-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.14 (s, 1H), 2.74 (t, 2H), 2.67 (m, 1H), 1.91 (m, 4H), 1.77 (m, 3H), 1.22-1.56 (m, 5H), 0.98 (t, 3H). MS *m/z:* 230.4 (M+1), 100%.

EXAMPLE 3.

3: 4-cycloheptyl-6-(3-hydroxy-propyl)-pyrimidine-2-carbonitrile



A: 1, 3-dioxo-6-hydroxy-1-cycloheptyl-hexane

To a stirred suspension of sodium hydride (60% in parafin oil, 12.7 g) in diethyl ether (800 ml) at 0 °C was added ethanol (0.65 ml). To above mixture was then added gamma-butyrolactone (11.6 g), followed by the dropwise addition in 30 minutes of a diethyl ether solution (100 ml) of cyclo-heptyl methyl ketone (17.8 g). The mixture was allowed to stir at room temperature for 72 hours. Ethanol (20 ml) was then added to destroy excess sodium hydride, followd by addition of an aqueous solution of ammonium chloride (20 g in 300 ml water). The organic layer was separated and washed with diluted hydrochloric acid (0.1N, 500 ml), then with water (2 x 200 ml). The ether layer was then dried over sodium sulphate, whereupon solvent was removed under reduced pressure. The residue was columned on silica gel using petrol and ethyl acetate (1:1) as eluant to give 1,3-dioxo-6-hydroxy-1-cycloheptyl-hexane (3.6 g). ^{1}H NMR ($CDCl_3$): δ 15.50 (bs, 1H), 5.49 (s, 1H), 3.69 (t, 2H), 2.43 (t, 2H), 2.31 (m, 1H), 1.88 (m, 5H), 1.74 (m, 3H), 1.36-1.66 (m, 7H). MS *m/z*: 227.3 (M+1), 100%.

B: 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methylsulfanyl-pyrimidine

A mixture of 1,3-dioxo-6-hydroxy-1-cycloheptyl-hexane (3.6 g) and S-methyl isothiouronium iodide salt (4.5 g) was heated under N_2 at 130°C for 5 hours. After cooling to room temperature, triethylamine (10 ml) and methanol (10 ml) were added, and the mixture was heated to reflux with an oil bath at 85 °C for 4 hours. After removal of solvent and triethyl amine at reduced pressure, the residue was taken into ethyl acetate (100 ml) and water (100 ml). The organic layer was seperated, then washed with diluted hydrochloric acid (0.1N, 500 ml), followed with water (2 x 100 ml) and dried, whereupon solvent was removed under reduced pressure. The residue was columned on silica gel using petrol and ethyl acetate (1:1) as eluant to give 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methylsulfanyl-pyrimidine (1.6 g).

^{1}H NMR ($CDCl_3$): δ 6.65 (s, 1H), 3.70 (m, 2H), 2.78 (t, 2H), 2.73 (m, 1H), 2.55 (s, 3H), 2.43 (m, 1H), 1.43-2.00 (m, 14H). MS *m/z*: 281.1 (M+1), 100%.

C: 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methanesulphonyl-pyrimidine

To the solution of 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methylsulfanyl-pyrimidine (1.6 g) in a mixed solvent of methanol and water (30 ml, 10:1) was added OXONE (7.4 g). The mixture was stirred at room temperature for 8 hours, then diluted with ethyl acetate (200 ml). The mixture was washed with water (3 x 150 ml). Organic layer dried over sodium sulphate, solvent removed under reduced pressure to give 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methanesulphonyl-pyrimidine (1.53 g) as crude product which was used for next step without further purification.

^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H), 3.73 (t, 2H), 3.35 (s, 3H), 2.97 (t, 2H), 2.93 (m, 1H), 1.45-2.10 (m, 15H). MS *m/z*: 313.0 (M+1), 100%.

D: 4-cycloheptyl-6-(3-hydroxy-propyl)-pyrimidine-2-carbonitrile

To a stirred solution of 4-cycloheptyl-6-(3-hydroxy-propyl)-2-methane-sulphonyl-pyrimidine (1.53 g) in dimethylsulfoxide (10 mL), was added sodium cyanide (490 mg). The mixture was stirred at room temperature for 16 hours, then poured into ethyl acetate (50 mL) and washed with water (2 x 50 mL).
The organic layer was dried over sodium sulphate, evaporated at reduced pressure, and the residue was columned on silica gel using petrol and ethyl acetate (1:1) as eluant to give 4-cycloheptyl-6-(3-hydroxy-propyl)-pyrimidine-2-carbonitrile (0.73 g; compound **3**).

^{1}H NMR ($CDCl_3$): δ 7.18 (s, 1H), 3.71 (m, 2H), 2.89 (t, 2H), 2.85 (m, 1H), 1.48-2.05 (m, 15H). MS *m/z*: 260.3 (M+1), 100%.

EXAMPLE 4.

4: 4-cycloheptyl-6-(3-piperidin-1-yl-propyl)-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

A: 4-cycloheptyl-6-(3-oxo-propyl)-pyrimidine-2-carbonitrile

Dess-Martin periodinane (1.67 g) was added to a solution of 4-cycloheptyl-6-(3-hydroxy-propyl)-pyrimidine-2-carbonitrile (**3**, 0.73 g) in DCM (73 mL), and the resulting suspension was stirred at room temperature for 80 minutes. The mixture was diluted with DCM (30 mL), then washed with water (3 x 50 mL), dried over sodium sulphate, and evaporated at reduced pressure. Flash chromatography of the residue on silica afforded 4-cycloheptyl-6-(3-oxo-propyl)-pyrimidine-2-carbonitrile as a viscous oil (0.61 g).

^{1}H NMR ($CDCl_3$): δ 9.85 (s, 1H), 7.22 (s, 1H), 3.01-3.11 (2d, 4H), 2.85 (m, 1H), 1.47-1.98 (m, 12H). MS *m/z*: 258.1 (M+1), 100%.

B: 4-cycloheptyl-6-(3-piperidin-1-yl-propyl)-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

To 4-cycloheptyl-6-(3-oxo-propyl)-pyrimidine-2-carbonitrile (30mg) was added macroporous cyanoborohydride (74.4 mg, 2.35 mmol/g), acetonitrile (1 mL), piperidine (13.8 μL) and acetic acid (0.1 mL). The mixture was stirred and heated in a microwave at 150 °C for 10 minutes, then cooled and filtered. The filtrate was applied to a preparative-HPLC purification with acetonitrile/water containing 0.1% trifluoroacetic acid as eluant. Evaporation of the eluate at reduced pressure afforded 4-cycloheptyl-6-(3-piperidin-1-yl-propyl)-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt as a gum (21 mg).

^{1}H NMR ($CDCl_3$): δ 12.27 (bs, 1H), 7.20 (s, 1H), 3.65 (m, 2H), 3.10 (m, 2H), 2.88 (t, 2H), 2.85 (m, 1H), 2.63 (m, 2H), 2.26 (m, 2H), 1.32-2.10 (m, 18H). MS *m/z*: 327.5 (M+1), 100%.

The procedure described in Example 4 was further applied, using the appropriate amine derivatives, to prepare the compounds of Examples 5-30:

EXAMPLE 5.

4-cycloheptyl-6-[3-(4-pyridin-2-yl-piperazin-1-yl)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:2) salt

^{1}H NMR ($CDCl_3$): δ 8.24 (d, 1H), 7.80 (t, 1H), 7.19 (s, 1H), 6.93 (t, 1H), 6.86 (d, 1H), 4.02 (m, 4H), 3.40 (m, 4H), 3.19 (t, 2H), 2.91 (t, 2H), 2.85 (m, 1H), 2.41-2.78 (bs, 2H), 2.31 (m, 2H) 1.49-1.97 (m, 12H). MS *m/z*: 405.4 (M+1), 100%.

EXAMPLE 6.

4-cycloheptyl-6-[3-(4-phenyl-piperazin-1-yl)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 7.31 (t, 2H), 7.20 (s, 1H), 6.98 (t, 1H), 6.93 (d, 2H), 3.66 (m, 4H), 3.38 (m, 2H), 3.18 (t, 2H), 3.01 (m, 2H), 2.92 (t, 2H), 2.85 (m, 1H), 2.31 (m, 2H), 1.91 (m, 2H) 1.84 (m, 2H) 1.39-1.78 (m, 8H). MS *m/z*: 404.4 (M+1), 100%.

EXAMPLE 7.

4-[3-(4-benzyl-piperazin-1-yl)-propyl]-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 7.44 (m, 5H), 7.16 (s, 1H), 4.13 (s, 2H), 3.61 (m, 4H), 3.48 (m, 4H), 3.16 (t, 2H), 2.88 (t, 2H), 2.84 (m, 1H), 2.24 (m, 2H), 1.90 (m, 2H), 1.83 (m, 2H) 1.50-1.77 (m, 8H). MS *m/z*: 418.4 (M+1), 100%.

EXAMPLE 8.

4-cycloheptyl-6-[3-(3-diethylcarbamoyl-piperidin-1-yl)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 12.11 (bs, 1H), 7.18 (s, 1H), 3.65 (d, 1H), 3.54 (d, 1H), 3.26-3.45 (m, 5H), 3.13 (m, 2H), 3.01 (m, 1H), 2.87 (t, 2H), 2.82 (m, 1H), 2.68 (m, 1H), 2.27 (m, 2H), 2.13 (m, 1H), 1.79-2.05 (m, 6H), 1.49-1.78 (m, 9H), 1.20 (t, 3H), 1.11 (t, 3H). MS *m/z*: 426.1 (M+1), 100%.

EXAMPLE 9.

4-cycloheptyl-6-[3-(3-phenyl-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 13.11-13.38 (b, 1H), 7.15-7.40 (m, 6H), 3.96-4.18 (m, 1.5H), 3.84 (m, 0.5H), 3.74 (m, 0.5H), 3.59 (m, 0.5H), 3.39 (m, 0.5H), 3.27 (m, 2H), 3.16 (m, 0.5H), 2.78-3.03 (m, 4H), 2.60 (m, 0.5H), 2.45 (m, 0.5H), 2.15-2.39 (m, 3H), 1.48-2.00 (m, 12H). MS *m/z*: 389.3 (M+1), 100%.

EXAMPLE 10.

4-cycloheptyl-6-[3-(cyclohexylmethyl-amino)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.36 (bs, 2H), 7.20 (s, 1H), 3.02-3.18 (m, 3H), 2.77-2.99 (m, 5H), 2.21 (m, 2H), 1.41-1.98 (m, 14H), 1.08-1.35 (m, 5H), 0.88-1.06 (m, 3H). MS *m/z*: 355.4 (M+1), 100%.

EXAMPLE 11.

4-(3-benzylamino-propyl)-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.77 (bs, 2H), 7.29-7.41 (m, 5H), 7.13 (s, 1H), 3.95 (s, 2H), 2.94 (t, 2H), 2.76-2.86 (m, 3H), 2.10 (m, 2H), 1.77-1.93 (m, 4H), 1.48-1.74 (m, 8H). MS *m/z*: 349.5 (M+1), 100%.

EXAMPLE 12.

4-cycloheptyl-6-[3-(2-pyridin-2-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:2) salt

^{1}H NMR ($CDCl_3$): δ 10.63 (bs, 2H), 8.51 (d, 1H), 8.00 (m, 1H), 7.52 (m, 2H), 7.23 (s, 1H), 3.55 (m, 2H), 3.42 (m, 2H), 3.16 (t, 2H), 2.94 (t, 2H), 2.85 (m, 1H), 2.25 (m, 2H), 1.78-1.97 (m, 4H), 1.48-1.77 (m, 8H). MS *m/z*: 364.3 (M+1), 100%.

EXAMPLE 13.

4-{3-[(biphenyl-4-ylmethyl)-amino]-propyl}-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.77 (bs, 2H), 7.29-7.67 (m, 9H), 7.05 (s, 1H), 4.02 (s, 2H), 3.00 (t, 2H), 2.78 (m, 3H), 2.12 (m, 2H), 1.46-1.97 (m, 12H). MS *m/z*: 425.3 (M+1), 100%.

EXAMPLE 14.

4-cycloheptyl-6-[3-(4-pyridin-2-yl-benzylamino)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:2) salt

^{1}H NMR ($CDCl_3$): δ 9.85 (bs, 2H), 8.87 (bs, 1H), 8.19 (m, 1H), 7.90 (m, 3H), 7.63 (m, 3H), 7.16 (s, 1H), 4.14 (s, 2H), 3.10 (m, 2H), 2.84 (m, 3H), 2.18 (m, 2H), 1.76-1.96 (m, 4H), 1.45-1.74 (m, 8H). MS *m/z*: 426.3 (M+1), 47%.

EXAMPLE 15.

4-cycloheptyl-6-[3-(2-piperidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:2) salt

^{1}H NMR ($CDCl_3$): δ 7.23 (s, 1H), 3.42-3.79 (m, 6H), 3.14 (m, 2H), 2.68-3.00 (m, 5H), 2.24 (m, 2H), 1.38-2.09 (m, 18H). MS *m/z*: 370.4 (M+1), 91%.

EXAMPLE 16.

4-[3-(3-acetylamino-pyrrolidin-1-yl)-propyl]-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 12.95 (bs, 1H), 8.22 (bs, 1H), 7.22 (s, 1H), 4.87 (m, 1H), 3.92 (m, 1H), 3.68 (d, 1H), 3.19 (m, 2H), 3.04 (m, 1H), 2.79-2.98 (m, 4H), 2.53 (m, 1H), 2.29 (m, 2H), 2.20 (m, 1H), 1.98 (s, 3H), 1.47-1.96 (m, 12H). MS *m/z*: 370.3 (M+1), 100%.

EXAMPLE 17.

4-cycloheptyl-6-(3-cyclohexylamino-propyl)-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.28 (bs, 2H), 7.20 (s, 1H), 3.08 (m, 2H), 2.97 (m, 1H), 2.91 (t, 2H), 2.85 (m, 1H), 2.20 (m, 2H), 2.10 (m, 2H), 1.77-1.96 (m, 6H), 1.13-1.77 (m, 14H). MS *m/z*: 341.3 (M+1), 100%.

EXAMPLE 18.

4-cycloheptyl-6-[3-(pyridin-2-ylamino)-propyl]-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 16.63 (b, 1H), 10.26 (bs, 1H), 7.88 (t, 1H), 7.73 (d, 1H), 7.36 (s, 1H), 6.94 (d, 1H), 6.74 (t, 1H), 3.38 (m, 2H), 2.94 (t, 2H), 2.85 (m, 1H), 2.20 (m, 2H), 1.39-2.00 (m, 12H). MS *m/z*: 336.3 (M+1), 100%.

EXAMPLE 19.

(R,R)-4-[3-(2-benzyloxy-cyclopentylamino)-propyl]-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.81 (bs, 1H), 9.30 (bs, 1H), 7.20-7.43 (m, 5H), 7.14 (s, 1H), 4.54 (d, 1H), 4.44 (d, 1H), 4.19 (m, 1H), 3.39 (m, 1H), 3.09 (m, 2H), 2.85 (m, 1H), 2.81 (t, 2H), 1.44-2.27 (m, 20H). MS *m/z*: 433.4 (M+1), 100%.

EXAMPLE 20.

(S,S)-4-[3-(2-benzyloxy-cyclopentylamino)-propyl]-6-cycloheptyl-pyrimidine-2-carbonitrile trifluoroacetic acid (1:1) salt

^{1}H NMR ($CDCl_3$): δ 9.84 (bs, 1H), 9.26 (bs, 1H), 7.18-7.42 (m, 5H), 7.13 (s, 1H), 4.55 (d, 1H), 4.44 (d, 1H), 4.19 (m, 1H), 3.39 (m, 1H), 3.08 (m, 2H), 2.88 (m, 1H), 2.82 (t, 2H), 1.36-2.27 (m, 20H). MS *m/z*: 433.5 (M+1), 100%.

EXAMPLE 21.

4-Cycloheptyl-6-[3-(3-methyl-butylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H), 3.03-3.12 (br m, 2H), 2.91-3.00 (br m, 2H), 2.90 (t, 2H), 2.81-2.87 (m, 1H), 2.18-2.25 (m, 2H), 1.79-1.94 (m, 3H), 1.52-1.74 (m, 12H), 0.91 (d, 6H). MS *m/z* 329.3 (M+1), 97%.

EXAMPLE 22.

4-Cycloheptyl-6-(3-phenethylamino-propyl)-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.29-7.32 (m, 2H), 7.25 (s, 1H), 7.17-7.21 (m, 3H), 3.20-3.30 (br m, 2H), 3.03-3.17 (br m, 4H), 2.87-2.94 (br t, 2H), 2.79-2.86 (m, 1H), 2.18-2.28 (br m, 2H), 1.49-2.10 (m, 12H). MS *m/z* 363.3 (M+1), 95%.

EXAMPLE 23.

4-Cycloheptyl-6-[3-(2-morpholin-4-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.21 (s, 1H), 3.95-4.06 (br m, 4H), 3.50-3.73 (br m, 4H), 3.15-3.42 (br m, 6H), 2.90-3.00 (br m, 2H), 2.86 (br t, 1H), 2.17-2.28 (br m, 2H), 1.52-1.97 (m, 12H). MS *m/z* 372.0 (M+1), 100%.

EXAMPLE 24.

4-Cycloheptyl-6-{3-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-propyl}-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.21 (s, 1H), 3.73-3.84 (br m, 1H), 3.31-3.42 (br m, 1H), 2.07-3.24 (br m, 19H), 1.51-1.94 (m, 12H). MS *m/z* 370.3 (M+1), 100%.

EXAMPLE 25.

4-Cycloheptyl-6-[3-(2-pyrrolidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 3.63-3.79 (br m, 2H), 3.46-3.58 (br m, 2H), 3.13-3.25 (br m, 2H), 2.90-2.98 (br m, 2H), 2.82-2.89 (m, 1H), 2.10-2.30 (br m, 6H), 1.53-1.95 (m, 12H). MS *m/z* 356.1 (M+1), 100%.

EXAMPLE 26.

4-Cycloheptyl-6-[3-(2-pyridin-3-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 9.10 (br s, 1H), 8.61 (br s, 1H), 8.42 (br s, 1H), 7.89 (br s, 1H), 7.16 (s, 1H), 3.26-3.82 (br m, 4H), 3.06-3.20 (br m, 2H), 2.76-2.90 (br m, 3H), 2.12-2.21 (br m, 2H), 1.49-1.93 (m, 12H). MS *m/z* 364.1 (M+1), 100%.

EXAMPLE 27.

4-Cycloheptyl-6-[3-(2-pyridin-4-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 8.63-8.80 (br m, 2H), 7.84-8.00 (br m, 2H), 7.19 (s, 1H), 3.36-3.55 (br m, 4H), 3.10-3.26 (br m, 2H), 2.78-2.95 (br m, 3H), 2.12-2.26 (br m, 2H), 1.50-1.93 (m, 12H). MS *m/z* 364.3 (M+1), 81%.

EXAMPLE 28.

4-Cycloheptyl-6-[3-(3,3,3-trifluoropropylamino)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.19 (s, 1H), 3.22-3.31 (m, 2H), 3.10-3.20 (m, 2H), 2.82-2.96 (m, 3H), 2.61-2.74 (m, 2H), 2.19-2.30 (m, 2H), 1.50-1.97 (m, 12H). MS *m/z* 355.3 (M+1), 87%.

EXAMPLE 29.

4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-6-cycloheptyl-pyrimidine-2-carbonitrile

^{1}H NMR (MeOD): δ 7.49 (s, 1H), 4.08-4.20 (m, 1H), 3.40-3.87 (br m, 4H), 2.89-2.96 (m, 3H), 2.53-2.64 (m, 2H), 2.19-2.24 (m, 3H), 1.59-1.95 (m, 12H). MS *m/z* 328.3 (M+1), 100%.

EXAMPLE 30.

4-Cycloheptyl-6-[3-(3-diethylamino-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile

^{1}H NMR ($CDCl_3$): δ 7.18 (s, 1H), 4.23-4.41 (br m, 1H), 3.94-4.12 (br m, 2H), 3.67-3.79 (br m, 1H), 3.45-3.56 (br m, 1H), 3.12-3.36 (br m, 4H), 2.82-2.93 (m, 3H), 2.52-2.64 (br m, 2H), 2.20-2.32 (br m, 2H), 1.52-1.95 (m, 12H), 1.37 (t, 6H). MS *m/z* 384.3 (M+1), 100%.

EXAMPLE 31

Cathepsin K Assay Procedure:

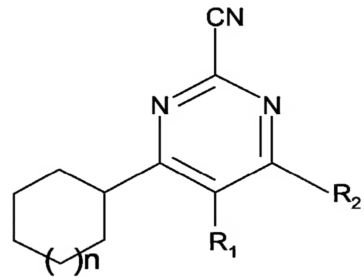
The inhibitory activity of the compounds of the invention was demonstrated *in vitro* by measuring the inhibition of recombinant human Cathepsin K as follows:

To a 384 well microtitre plate is added 5μl of a 100μM solution of test compound in assay buffer (100mM sodium acetate pH5.5, 5mM EDTA, 5mM dithiothreitol) with 10% dimethylsulfoxide (DMSO), plus 10μl of 100μM solution of the substratre Z-Phe-Arg-AMC (Bachem; 7-amido-coumarine derivative of the dipeptide N-benzyloxy-carbonyl-Phe-Arg-OH) in assay buffer and 25μl of assay buffer. 10μl of a 1mg/l solution of activated recombinant human cathepsin K, in assay buffer, is then added to the well, yielding a final inhibitor concentration of 10μM.

Enzyme activity is determined by measuring the fluorescence of the liberated aminomethylcoumarin at 440nM using 390nM excitation, at 10 minutes. Percentage enzyme activity is calculated by comparison of this activity to that of a solution containing no inhibitor. Compounds are subsequently subjected to a dose response curve analysis in order to determine IC_{50} values for active compounds (where IC_{50} is the concentration of test compound causing 50 % inhibition of the enzymatic activity). Compounds of the invention typically have a pIC_{50} (negative logarithm of the IC_{50} concentration) for inhibition of human cathepsin K of more than 6, preferably more than 7 such as for the compounds of Examples **1**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **17**, **23**, and most preferably a pIC_{50} of more than 8, such as for the compounds of Examples **12**, **15**, **25**, and **30**.

Claims.

1. A 4-cycloalkyl-pyrimidine-2-carbonitrile derivatives having the general formula I



Formula I

wherein

n is 0, 1, 2 or 3;

R_1 is H or (C_{1-6})alkyl;

R_2 is (C_{1-6})alkyl, optionally substituted with one or more halogens, OH, (C_{1-4})-alkyloxy or NR_3R_4 ;

R_3 and R_4 are independently H, (C_{1-4})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl(C_{1-4})-alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-9})heteroaryl, (C_{2-9})heteroaryl(C_{1-4})alkyl or (C_{1-4})alkyl substituted with a 4-8 membered saturated heterocyclic ring comprising 1-3 heteroatoms selected from O, S and NR_5; or

R_3 and R_4 together with the nitrogen to which they are bound form a 4-8 membered saturated heterocyclic ring, which ring optionally comprises NR_5, and which ring is optionally substituted with (C_{6-10})aryl, (C_{6-10})aryloxy, (C_{6-10})aryl(C_{1-4})-alkyloxy, (C_{2-9})heteroaryl, NR_6,R_7, $CONR_6R_7$ or NR_6COR_7;

R_5 is H, (C_{1-4})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-4})alkyl, (C_{2-5})heteroaryl or (C_{2-5})-heteroaryl(C_{1-4})alkyl;

R_6 and R_7 are independently H or (C_{1-4})alkyl;

or a pharmaceutically acceptable salt thereof.

2. The 4-cycloalkyl-pyrimidine-2-carbonitrile derivative according to claim 1, wherein R_1 is H and R_2 is (C_{1-6})alkyl substituted with OH, one or more halogens, (C_{1-4})-alkyloxy or NR_3R_4.

3. The 4-cycloalkyl-pyrimidine-2-carbonitrile derivative according to claim 1 or 2, wherein R_2 is n-propyl substituted at the 3-position with NR_3R_4.

4. The 4-cycloalkyl-pyrimidine-2-carbonitrile derivative according to claim 3, wherein the 4-cycloalkyl group is cycloheptyl (n=2).

5. The 4-cycloalkyl-pyrimidine-2-carbonitrile derivative of formula I of claim 1 which is selected from:
- 4-cycloheptyl-6-[3-(3-phenyl-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-pyridin-2-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-piperidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-(3-cyclohexylamino-propyl)-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-morpholin-4-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile;
- 4-cycloheptyl-6-[3-(2-pyrrolidin-1-yl-ethylamino)-propyl]-pyrimidine-2-carbonitrile; and
- 4-cycloheptyl-6-[3-(3-diethylamino-pyrrolidin-1-yl)-propyl]-pyrimidine-2-carbonitrile; or a pharmaceutically acceptable salt thereof.

6. A 4-cycloalkyl-pyrimidine-2-carbonitrile derivative of any one of claims 1-5 for use in therapy.

7. Use of a 4-cycloalkyl-pyrimidine-2-carbonitrile derivative of any one of claims 1-5 for the preparation of a medicament for the treatment of osteoporosis, atherosclerosis and related disorders.

8. A pharmaceutical composition comprising a 4-cycloalkyl-pyrimidine-2-carbonitrile derivative of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable auxilliaries.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/055091

A. CLASSIFICATION OF SUBJECT MATTER
C07D239/28 C07D401/12 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/020278 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; ALTMAN, EVA; HAYAKAWA, KENJI; IWASA) 13 March 2003 (2003-03-13) cited in the application the whole document -----	1-8
A	WO 2004/020441 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; ALTMANN, EVA; BETSCHART, CLAUDIA; H) 11 March 2004 (2004-03-11) cited in the application the whole document -----	1-8
A	WO 2004/000819 A (ASTRAZENECA AB; BAILEY, ANDREW; PAIRAUDEAU, GARRY; PATEL, ANIL; THOM,) 31 December 2003 (2003-12-31) cited in the application the whole document -----	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2006	28/03/2006

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP2005/055091

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